DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment filed August 17, 2009 has been entered. Claims 1-9, 11-41, 45-46 and 50-68 have been canceled. Claims 10, 42-44 and 47-49 have been amended. Claims 69-70 have been added.

Claims 10, 42-44, 47-49 and 69-70 are under examination.

Rejections Withdrawn

2. In view of Applicant's amendment and response the following rejections have been withdrawn:

(a) rejection of claims 10, 14, 42-49 and 68 under 35 U.S.C. 112 first paragraph (written description), pages 2-7, paragraph 2.

(b) rejection of claims 10, 14, 42-49 and 68 under 35 U.S.C. 112 first paragraph (scope of enablement), pages 8-12, paragraph 3.

(c) rejection of claims 10, 14, 42-49 and 68 under 35 U.S.C. 112 second paragraph pages 12-14, paragraph 4.

New Grounds of Rejection

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 10 and 42-44 are rejected under 35 U.S.C. 101 because the claimed invention the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Independent claim 10 is a complex of a ligand and a polypeptide, wherein the polypeptide comprises the isolated amino acid sequence selected from (i) the amino acids 40-60 of SEQ ID No:7 (mouse synaptotagmin II botulinum toxin serotype B (BoNT/B)-binding domain) and (ii) the amino acids 40-60 of SEQ ID NO:9 (rat synaptogmin II botulinum toxin serotype (BoNT/B)-binding domain) wherein the ligand is BoNT/B and binds to the polypeptide at amino acids 40 to 60 of SEQ ID NO:7 or SEQ ID NO:9.

The claimed invention is directed to a complex of a ligand and a polypeptide wherein the ligand is BoNT/B. The specification asserts a utility for the polypeptide. The specification asserts an utility for the BoNT/B which is the ligand. The instant specification lacks a specific and substantial utility for the claimed complex of a ligand and a polypeptide. The instant specification discloses a method for reducing BoNT/B cellular toxicity in target cells such as neurons by reducing the synaptotagmin I (syt I) and synaptotagmin II (syn II) protein levels in target cells by inhibiting BoNT/B related cellular functions of syt I and syn II (page 12). The specification teaches a method for

screening for agents that block BoNT/B and polypeptide binding (page 14). The specification teaches using the polypeptide of the complex to detect BoNT/B or *Clostridium botulinum* (page 17). The utilities disclosed in the specification *only* disclose utilities for the polypeptide or the ligand, BoNT/B *but not a complex of a ligand and a polypeptide wherein the ligand is BoNT/B.*

4. Claims 47-49 and 69-70 are rejected under 35 U.S.C. 101 because the claimed invention the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Independent claim 47 is a complex of a ligand and a polypeptide, wherein the polypeptide comprises the isolated amino acid sequence selected from (i) the amino acids 40-60 of SEQ ID No:7 (mouse synaptotagmin II botulinum toxin serotype B (BoNT/B)-binding domain) and (ii) the amino acids 40-60 of SEQ ID NO:9 (rat synaptogmin II botulinum toxin serotype (BoNT/B)-binding domain) wherein the ligand is BoNT/B and binds to the polypeptide at amino acids 40 to 60 of SEQ ID NO:7 or SEQ ID NO:9 and reduces binding of BoNT/B to the polypeptide, and wherein the complex is located *in vivo* in a mammal.

Independent claim 60 is a complex of a ligand and a polypeptide, wherein the polypeptide comprises the isolated amino acid sequence selected from (i) the amino acids 40-60 of SEQ ID No:7 (mouse synaptotagmin II botulinum toxin serotype B (BoNT/B)-binding domain) and (ii) the amino acids 40-60 of SEQ ID NO:9 (rat synaptogmin II botulinum toxin serotype (BoNT/B)-binding domain) wherein the ligand is

an antibody against said amino acid sequence and binds to the polypeptide at amino acids 40 to 60 of SEQ ID NO:7 or SEQ ID NO:9, thereby reducing binding of BoNT/B to the polypeptide.

The claimed invention is directed to a complex of a ligand and a polypeptide wherein the ligand is and antibody that binds to the polypeptide at amino acids 40 to 60 of SEQ ID NO:7 or at amino acids 40 to 60 of SEQ ID NO:9 and reduces binding of BoNT/B to the polypeptide. The specification asserts a utility for the polypeptide. The specification asserts an utility for the antibody which is the ligand. The instant specification lacks a specific and substantial utility for the claimed complex of a ligand and a polypeptide. The instant specification discloses a method for reducing BoNT/B cellular toxicity in target cells such as neurons by reducing the synaptotagmin I (syt I) and synaptotagmin II (syn II) protein levels in target cells by inhibiting BoNT/B related cellular functions of syt I and syn II (page 12). The specification teaches a method for screening for agents that block BoNT/B and polypeptide binding (page 14). The specification teaches using the polypeptide of the complex to detect BoNT/B or *Clostridium botulinum* (page 17). The utilities disclosed in the specification only disclose utilities for the polypeptide or the ligand which is the antibody that binds to the polypeptide at amino acids 40 to 60 of SEQ ID NO:7 or at amino acids 40 to 60 of SEQ ID NO:9 and reduces binding of BoNT/B to the polypeptide but not a complex of a antibody and a polypeptide. The instant specification has failed to show that claimed complex comprising the polypeptide and the antibody that binds to the polypeptide at amino acids 40 to 60 of SEQ ID NO:7 or at amino acids 40 to 60 of SEQ ID NO:9 can

reduce binding of BoNT/B to the polypeptide. Page 14 of the instant specification discloses monoclonal and polyclonal antibodies that are specific for the BoNT/B binding domains of syt I and syt II to block the BoNT/B binding sites on syt I and syt II. The antibody blocks the binding of the BoNT/B binding sites on syt I and syt II and *not* the complex comprising the antibody and a polypeptide. The instant specification has not established that the claimed complex would be capable of reduce binding of BoNT/B to the polypeptide.

In regards to claim 47 which recites the limitation "...wherein the complex is located in vivo in a mammal", this claim and the claims which depend from claim 47 are not supported by either a credible asserted utility or a well-established utility.

Neither the specification as filed nor any art of record discloses or suggests any specific property or activity for the animals such that a utility would be well established for the animals.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 10, 42-44 and 69-70 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

6. Claims 47-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Independent claim 47 is a complex of a ligand and a polypeptide, wherein the polypeptide comprises the isolated amino acid sequence selected from (i) the amino acids 40-60 of SEQ ID No:7 (mouse synaptotagmin II botulinum toxin serotype B (BoNT/B)-binding domain) and (ii) the amino acids 40-60 of SEQ ID NO:9 (rat synaptogmin II botulinum toxin serotype (BoNT/B)-binding domain) wherein the ligand is BoNT/B and binds to the polypeptide at amino acids 40 to 60 of SEQ ID NO:7 or SEQ

ID NO:9 and reduces binding of BoNT/B to the polypeptide, and wherein the complex is located *in vivo* in a mammal.

Applicants broadly claim a transgenic animal. These claims read on a complex comprising a polypeptide and a ligand within a transgenic animal given that the term "isolated" is not denoted in describing the transgenic animal. The breadth of the claim reads on the implementation of the transgenic animal in *in vivo* assays.

The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics. For example, Overbeek *("Factors affecting transgenic animal production," Transgenic Animal Technology, 1994, pages 96-98)* taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). Wall (*Theriogenology, 1996,Vol. 45, pp. 57-68)* teaches that the art of transgenic animals has for many years stated that the unpredictability lies, in part, with the site or sites of transgene integration into the target genome and that "the position effect" as well as unidentified control elements are recognized to cause aberrant expression of a transgene. The elements of the particular construct used to make transgenic animals are also held to be critical, and they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc., see Houdebine, *(J. Biotech. Vol. 34, 1994, pages 269-287, specifically page 281).* Furthermore, transgenic animals are regarded to have within their cells, cellular mechanisms that prevent expression of the transgene, such as

methylation or deletion from the genome, see Kappel, (*Current Opinions in Biotechnology, Vol. 3, 1992, pp. 548-553).*

Well-regulated transgene expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues. See Cameron, *(Molec. Biol. 7, 1997, pages 253-265, specifically page 256, col. 1 -2, bridg. parag.).* Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct. See Cameron, *(Molec. Biol. 7, 1997, page 256, lines 3-9).* With regard to the importance of promoter selection, Niemann, *(Transg. Res. 7, 1997, pages 73-75),*states "that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health" (pages 73-75, specifically page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4).

Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. Mullins, *(Hypertension, Vol. 22, 1993, pp. 630-633)* states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes. For example, several animal models for human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins (*Nature, Vol. 344, 1990, 541-544)* produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer *(Cell, Vol. 63,*

1990, 1099-1112) describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. See Mullins *(EMBO J., vol. 8, 1989, pages 4065-4072; Taurog et al, Jour. Immunol., Vol. 141, 1988, pages 4020-4023).* Mullins *(J. Clin. Invest. Vol. 98, 1996. pages S37-S40)* disclose that the use of non-murine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another. Thus, at the time of filing, the phenotype of a transgenic cell contained within any animal was unpredictable and could not be prepared for any species.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect predicting the phenotype of

transgenics., 3) the reference cited above convey the state of the art regarding unpredictability of determining the phenotypes of trangenics, and 4) no working examples present in the specification regarding predicting the phenotypes of transgenic. 6) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art could not predict the phenotype of transgenics because of the lack of guidance in the art and in the instant specification in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

Status of the Claims

7. No claims allowed.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to VANESSA L. FORD whose telephone number is (571)272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0756. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/
Examiner, Art Unit 1645
October 20, 2009